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SPECT-CT localization of axillary sentinel lymph nodes for radiotherapy of early breast cancer

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ABSTRACT

Purpose: To evaluate the opportunities of single photon emission tomography/computerized tomography (SPECT-CT) for localization of axillary sentinel lymph nodes (ASLNs) and subsequent radiotherapy planning in women with early breast cancer.
Material and methods: Individual topography of ASLN was determined in 151 women with clinical T1-2N0M0 breast cancer. SPECT-CT visualization of ASLNs was initiated 120 min after intra-peritumoral injection of 99mTc-radiocolloids. Doses absorbed by virtual ASLNs after the whole breast irradiation with standard and extended tangential fields were calculated on a treatment planning station.
Results: SPECT-CT demonstrated a large variability of ASLN localization. They were detected in the central subgroup in 94 (61%) patients, in pectoral – in 77 (51%), and in interpectoral – in 4 (3%) patients. Sentinel lymph nodes "lying on the chest" were revealed in 35 (23%) cases.
We found that with standard tangential fields coverage of ASLNs was obtained only in 20% of evaluated women. Extended tangential fields can effectively irradiate ASLNs localized in all axillary sub-regions with the exception of ASLNs "lying on the chest".
Conclusion: SPECT-CT mapping of ASLNs in women with cT1-2N0M0 breast cancer reveals their variable localization. This information can be important for planning of radiation treatment in women that underwent breast conserving surgery without an axillary surgery.

1. Background

Results of randomized trials indicate that radiation therapy is an effective alternative to the axillary lymph node dissection in patients with breast cancer without clinical signs of metastatic involvement of regional lymph nodes (LNs).[1–3]

Due to the orderly progression of breast cancer from primary tumour to sentinel LNs (SLNs) these nodes can be considered as the main target for regional radiotherapy.[4] Furthermore, in some women with early breast cancer, irradiation of axillary SLNs (ASLNs) may be assumed as necessary and sufficient. It has been mentioned in several papers that ASLN can be effectively irradiated by tangential fields.[5,6] At the same time, it has been reported that the variability in SLNs topography can cause significant decrease in the dose absorbed by axillary LNs.[7,8]

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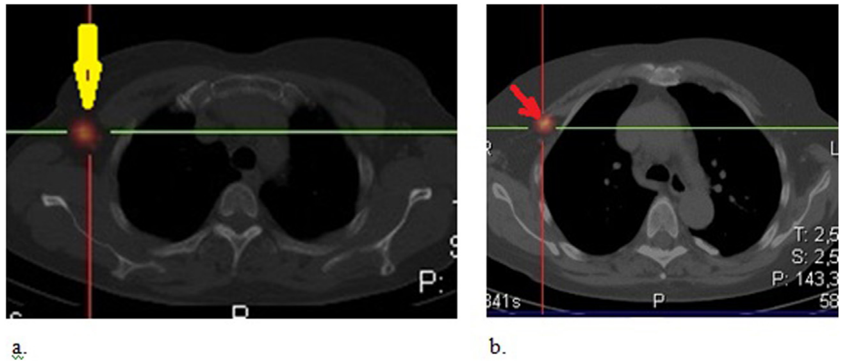

Fig. 1 – SPECT-CT axial views obtained after intratumoral injection of ^{99m}Tc-radiocolloids. (a) Sentinel lymph node located in the apical subgroup of axillary lymph nodes (big yellow arrow). (b) Sentinel lymph node that corresponds to Sorgius lymph node (red arrow).

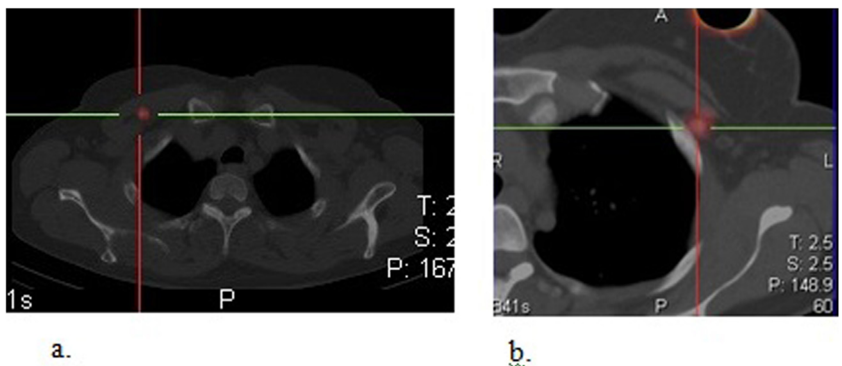

Fig. 2 – Fused SPECT-CT axial images of pectoral sentinel lymph nodes. (a) Sentinel lymph node located between the pectoral muscles. (b) Subpectoral sentinel lymph node.

Most of prior studies on axillary coverage by tangential fields used radiopaque markers placed at sites of the removed LNs. It was shown that individual patterns of lymphatic drainage and SLNs localization could be effectively determined by SPECT-CT examinations performed after intratumoral injection of radiocolloids.

Aim To assess individual variability of ASLNs localization in women with breast cancer and to determine the way this information can be used for treatment planning when considering simultaneous irradiation of the breast and ASLNs.

2. Material and methods

Between November 2013 and June 2015 SPECT-CT localization of SLNs was performed in 186 non-treated women with cT1-2N0 breast cancer. In all patients, the results of clinical and instrumental examinations indicated no evidence of regional LNs metastatic invasion. This single-center prospective study was approved by Institutional Ethical Committee. Informed consents were obtained from all women before including them into the study.

The SPECT-CT visualization of ASLNs was initiated 120 min after intra-peritumoral injection of 0.2–0.4 ml (100–300 MBq) of ^{99m}Tc labeled radiocolloids with particle size varied between 300 and 1000 nm. The large sizes of labeled radiocolloids permit preferential visualization of ASLNs without concomitant accumulation of this compound in the second-echelon LNs.

SPECT-CT examinations were performed with a high resolution hybrid system (Symbia T16, Siemens, Germany) supported by a low-energy high-resolution collimator. The acquisition of the images was performed with a patient in a position similar to the treatment position with the hands abducted above the head.

SPECT-CT images were evaluated by an experienced nuclear medicine specialist and radiation oncologist. They determined anatomical location and the number of visualized ASLNs. Taking into account that there is no conventional classification for various subgroups of axillary LNs in our study, we distinguished 5 axillary LN subgroups depending on their relationships with vessels and walls of the axillary cavity.[9] The central LNs are embedded in adipose tissue in the center of the axilla (Fig.1a). Pectoral LNs are located behind and along the free border of the pectoralis major muscle (Sorgius LN, Fig. 1b), as well as along the lower border of the pectoralis minor muscle. Parts of them are located in the chest wall along the lateral thoracic vessels (Fig. 2). The lateral subgroup of LN is positioned on the outer wall of the axilla below the level of the axillary vein. Subscapular subgroup of LNs lies on the posterior wall of the axillary cavity along the subscapular vessels (Fig. 3). The apical subgroup of LNs occupies the apex of the

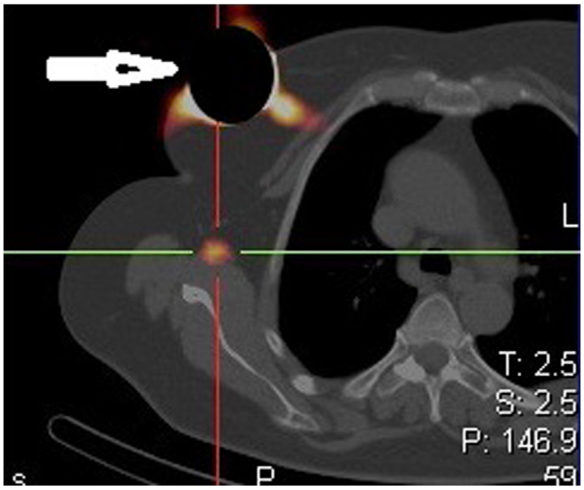

Fig. 3 – Sentinel lymph node visualized in subscapular region (injection site marked by a white arrow).

axilla at the level of the upper border of the pectoralis minor muscle and along the inferio-medial side of the axillary vein (Fig. 4). Subclavian LNs were included into the apical subgroup.

Additionally, the interpectoral LNs and those located in the vicinity of the chest wall were separately described. This subgroup of axillary LNs is represented by subpectoral LNs visualized behind the pectoral muscles at the level of the first and second intercostal spaces (Fig. 2b), and pectoral LNs, which are located in the vicinity of the chest wall (Fig. 5) along the lateral thoracic vessels (at the level of the third and fourth intercostal spaces).

To study the feasibility of the SLN irradiation by standard tangential fields, we took routine treatment plans of 10 consecutive patients with early breast cancer and then performed modeling of different treatment techniques evaluating absorbed doses in various subgroups of potential SLN. All 10 women underwent breast conserving surgery and were candidates for the whole breast radiotherapy with tangential fields. Breast volume in all 10 women was estimated as small or medium and varied between 186 cm^3 and 330 cm^3. Routinely, all patients were simulated in the treatment position. They were placed supine with the ipsilateral arm secured with the immobilization device. Tangential fields were designed in accordance with the following borders: cranial - 1–2 cm above the contour of the breast, caudal - 1–2 cm below the inframammary fold, anterior - 0.5 cm away from the breast contour, posterior - along the edge of the lateral costal arch, lateral - along the mid axillary line, and medial - at the sterno-clavicle joint.

Simulation was followed by cone beam computed tomography and, then, the entire set of data was transmitted to 3D planning system («Oncentra», Elekta, Sweden). CT of every woman was used as a model for virtual simulation of different radiotherapy techniques with different radiotherapy fields. In the treatment planning system, on CT slices of each of 10 models additional areas of interest were outlined around a singular LN which corresponded to SLN of the above mentioned axillary LN subgroups. LNs that represented every subgroup of axillary LNs were drawn in accordance with their relation to the corresponding vessels. These representatives of SLN of 5 above mentioned subgroups were called “virtual SLN”.

After planning a standard tangential irradiation of the breast (25 fraction of 2 Gy), we evaluated the absorbed dose in all above mentioned virtual SLNs: central, pectoral, interpectoral subregions and SLNs located in the vicinity of the chest wall. In our study, pectoral SLNs were represented by LNs near the border of the pectoralis major muscle (Sorgius LN). Lymph nodes located in the vicinity of the chest wall were examined separately and were subdivided into subpectoral SLNs (at the level of the first and second intercostal spaces) and LNs lying along lateral thoracic vessels (at the level of the third and fourth intercostal spaces).

At the next stage, extended (modified) tangential fields were generated for each woman using the same cone beam CT data. For this 3D treatment plan, the superior radiation field border was set at the inferior margin of the humeral head. Remaining borders were similar to those for standard tangents. Gantry and collimator angles were slightly modified in order to improve the coverage of LNs and minimize a dose to the lung.

Finally, after standard and extended tangential fields, we generated 3D treatment plans for intensity modulated radiation therapy (IMRT) for all 10 women. We used a forward planning technique. Breast tissue and SLN of every axillary subregion were determined as CTV with prescribing dose homogeneity between 95% and 110%. Constraints to critical organs were as follows: mean dose to the ipsilateral lung below 9 Gy, V20Gy<10%, mean dose to the heart below 7 Gy,

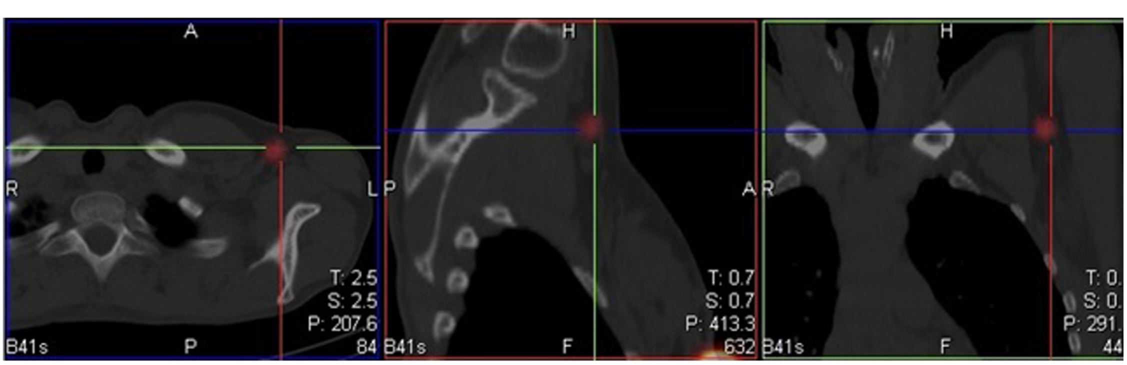

Fig. 4 – SPECT-CT images of the apical sentinel lymph nodes (axial, sagittal and coronal views).

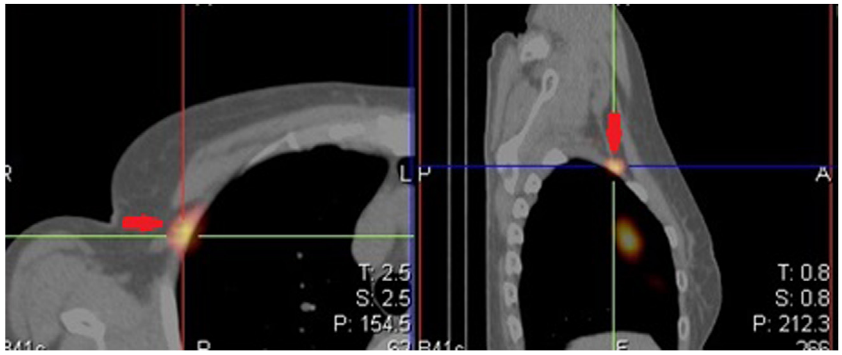

Fig. 5 – Fused SPECT-CT images in transverse and sagittal views, showing pectoral sentinel lymph node located "on the thoracic wall" (arrow).

Table 1 – Localization of visualized sentinel lymph nodes according to various axillary subgroups.

Localization of sentinel lymph nodes	Absolute number of observations	Relative frequency (in 151 women with visualized axillary sentinel nodes)
Central only	63	41%
Central + pectoral	21	14%
Central + pectoral + apical	4	3%
Central + lateral	1	1%
Central + subscapular	5	3%
Pectoral only	48	31%
Pectoral + apical	4	3%
Lateral only	5	3%

V20Gy<10%, V30Gy<5%. Thus, the task of delivering an adequate dose to the breast tissue and to all above mentioned virtual SLNs, first of all to SLNs "on the chest wall", was solved.

3. Results

A successful SPECT-CT visualization of SLNs was obtained in 151 (81%) out of 186 examined patients. As could be expected, SLNs were most frequently identified in the central subgroup of axillary LNs (94 patients; 62%). In 116 women SLNs were detected in only one subgroup of axillary nodes, in other 35 patients they were mentioned in two or more subgroups (Table 1). Sentinel LNs of the central subgroup were only those accumulating radiocolloids in 63 cases (41%), although in other observations we revealed a combination of SLNs in the central and other subgroups of axillary LNs. Somewhat less frequently, in 77 (50%) women, SLNs were located in the pectoral subgroup of LNs. In 48 (31%) patients, it was presented only as SLN of this subgroup, in the rest of them - by a combination with other subgroups. The SLN location close to the chest wall ("on the chest wall") was detected in 35 (23%) out of 151 patients, among them 17 (11%) patients presented with SLNs visualized in the subpectoral subgroup at the level of the first-second intercostal spaces. In other 18 (12%) patients, they were located at the level of the third and fourth intercostal spaces along the **a.** thoracica lateralis. It was mentioned that visualization of subpectoral SLNs at the first and second intercostal spaces in 14 (82%) cases was accompanied by the detection of SLN located near the border of the pectoralis major muscle (Sorgius LN) and/or by SLN in the central subgroup. Such a combination was found only in 7 (39%) out of 18 patients with SLN localization "on the chest wall" at the third or fourth intercostal spaces.

In 4 of 151 evaluated women, ASLNs were visualized in the interpectoral space. In 15 cases SPECT-CT detected ASLNs in the subscapular and apical regions. In all cases, their detection by SPECT-CT was accompanied by visualization of LNs in the central or pectoral subgroups.

Radiotherapy plans for the whole breast irradiation by standard tangential fields were generated for 10 patients (Table 2). Analysis of this plans demonstrated that the mean dose absorbed by SLNs defined in the central and subpectoral regions, as well as by SLNs located close to the edge of the chest wall at the third-fourthintercostal spaces, did not exceed 4.8 Gy, i.e. it was significantly lower than tumoricidal radiation dose. The mean dose delivered to Sorgius LN which represented SLN of the pectoral subgroup amounted to 46.6 Gy–52.1 Gy in two patients and did not exceed 25.5 Gy in 8 patients. The mean dose absorbed by the SLNs located in the projection of the lateral subgroup was 53 Gy in one patient and did not exceed 2.7 Gy in 9 patients. The mean dose delivered to the interpectoral SLNs was 42.5 Gy in one case and less than 33.3 Gy in 9 patients.

3D treatment plans for irradiation of the breast with extended (modified) tangential fields were generated with the account for topography of different SLNs defined in various axillary LN subgroups. The main goal of these treatment plans was the irradiation of the remaining breast tissue and ASLNs of different localizations. The mean doses delivered to SLNs by extended tangential fields are presented in Table 3. First of all, it should be noted that the mean doses delivered to SLNs of

Table 2 – Mean dose absorbed by virtual sentinel lymph nodes located in various axillary subgroups. 3D modeling of breast radiotherapy using standard tangential fields.

Case no. (Name)	Cent.[a]	Pect[a] (S)	Pect[a] (Th II)	Pect[a] (Th III)	Pect[a] (Th IV)	IP[a]	Lat[a]	Lung (V20 Gy; %)
1 (N)	4.3 (8.6%)	52.1 (104.2%)	2.9 (5.8%)	1.8 (3.6%)	1.7 (3.4%)	33.2 (6.64%)	53.1 (106.2%)	1,3 (2.6%)
2 (M)	0.6 (1.2%)	0.8 (1.6%)	0.7 (1.4%)	1.3 (2.6%)	2.5 (5%)	0.9 (1.8%)	0.8 (1.6%)	0
3 (L)	2.6 (5.2%)	25.5 (51%)	1.3 (2.6%)	1.1 (2.2%)	1.2 (2.4%)	15.1 (30.2%)	6.4 (12.8%)	0
4 (C)	0.5 (1%)	0.4 (0.8%)	0.7 (1.4%)	0.9 (1.8%)	0.9 (1.8%)	0.8 (1.6%)	0.5 (1%)	0
5 (MA)	1.2 (2.4%)	46.6 (93.2%)	2.4 (4.8%)	1.2 (2.4%)	2.3 (4.6%)	5.8 (11.6%)	6.9 (13.8%)	0
6 (R)	0.8 (1.6%)	1.2 (2.4%)	1.2 (2.4%)	1.1 (2.2%)	1.2 (2.4%)	10 (20%)	0.7 (1.4%)	0
7 (T)	1.4 (2.8%)	19.2 (38.4%)	1.9 (3.8%)	1.8 (3.6%)	2.9 5.8%)	4.6 (9.2%)	1.1 (2.2%)	0
8(Z)	3.4 (6.8%)	21.9 43.8%)	3.9 (7.8%)	2.7 (5.4%)	4.8 (9.6%)	42.5 (85%)	2.7 (5.4%)	1%
9 (A)	0.6 (1.2%)	0.5 (1%)	0.7 (1.4%)	0.6 (1.2%)	0.8 (1.6%)	0.7 (1.4%)	0.9 (1.8%)	0
10 (MI)	0.7 (1.4%)	1.1 (2.2%)	0.6 (1.2%)	0.8 (1.6%)	1.2 (2.4%)	1.5 (3%)	0.4 (0.8%)	1.4%

Cent, virtual sentinel lymph node localized in the central subgroup.
Pect (S), virtual sentinel lymph node represented by Sorgius lymph node localized in the pectoral subgroup.
Pect (Th II) virtual subpectoral sentinel lymph node localized in the pectoral subgroup close to the thoracic wall (opposite to II rib).
Pect (Th III) virtual sentinel lymph node localized in the pectoral subgroup close to the thoracic wall (opposite to III rib).
Pect (Th IV) virtual sentinel lymph node localized in the pectoral subgroup close to the thoracic wall (opposite to IV rib).
IP, virtual intrapectoral sentinel lymph node localized between pectoral muscles.
Lat, virtual sentinel lymph node localized in the lateral subgroup.
Lung (V20Gy; %), relative volume (%) of the ipsilateral lung absorbed the dose above 20 Gy.
[a] Absorbed dose in Gy (absorbed dose in percents of prescribed 50 Gy).

Table 3 – Mean dose absorbed by virtual sentinel lymph nodes located in various axillary subgroups. 3D modeling of breast radiotherapy using modified (high) tangential fields.

Case no. (Name)	Cent.	Pect (S)	Pect (Th II)	Pect (Th III)	Pect (Th IV)	IP	Lat	Lung (V20Gy;%)
1 (N)	45.3 (90.6%)	52.1 (104.2%)	43.9 (87.8%)	14.5 (29%)	4.8 (9.6%)	51.4 (102.8%)	47.3 (94.6%)	6.7%
2 (M)	43.5 (87%)	46.7 (93.4%)	41.3 (82.6%)	18.2 (36.4%)	45.2 (90.4%)	45.8 (91.%)	42.2 (84.4%)	12.9%
3 (L)	45.9 (91.8%)	50.4 (100.8%)	44 (88%)	3.2 (6.4%)	3.1 (6.2%)	50.1 (100.2%)	31 62%	13.4%
4 (C)	40 (80%)	41.1 (82.2%)	40.3 (80,6%)	22.2 (44.4%)	7.3 (14.6%)	42.3 (84.6%)	41.6 (83.2%)	10%
5 (MA)	45.2 (90.4%)	56.4 (112.8%)	45.6 (91.2%)	7.2 (14.4%)	25.9 (51.8%)	47.7 (95.4%)	43.1 (86.2%)	6.2%
6 (R)	42.7 (85.4%)	49 (98%)	49.4 (98.8%)	41.8 (83.6%)	10.3 (20.6%)	52 (104%)	40.6 (81.2%)	9.8%
7 (T)	48.5 (91.6%)	53.1 (106.2%)	46.2 (92.4%)	8.3 (16.6%)	19.1 (38.2%)	50.2 (100.4%)	42.8 (85.6%)	13%
8(Z)	43.2 (86.4%)	48 (96%)	44.3 (88.6%)	44.3 (88.6%)	41.2 (82.4%)	47.2 (94.4%)	45.3 (90.6%)	19%
9 (A)	35.8 (71.6%)	45.7 (91.4%)	40.2 (80.4%)	2.2 (4.4%)	2.4 (4.8%)	44.7 (89.4%)	40.1 (80.2%)	11.5%
10 (MI)	47.8 (95.6%)	52.5 (105%)	43.4 (86.8%)	17.5 (35%)	8 (16%)	51.7 (103.4%)	26.2 (52.4%)	8.2%

Cent, virtual sentinel lymph node localized in the central subgroup.
Pect (S), virtual sentinel lymph node represented by Sorgius lymph node localized in the pectoral subgroup.
Pect (Th II) virtual subpectoral sentinel lymph node localized in the pectoral subgroup close to the thoracic wall (opposite to II rib).
Pect (Th III) virtual sentinel lymph node localized in the pectoral subgroup close to the thoracic wall (opposite to III rib).
Pect (Th IV) virtual sentinel lymph node localized in the pectoral subgroup close to the thoracic wall (opposite to IV rib).
IP, virtual intrapectoral sentinel lymph node localized between pectoral muscles.
Lat, virtual sentinel lymph node localized in the lateral subgroup.
Lung (V20Gy; %), relative volume (%) of the ipsilateral lung absorbed the dose above 20 Gy.
*Absorbed dose in Gy (absorbed dose in percents of prescribed 50 Gy).

interpectoral, subpectoral or pectoral (Sorgius LN) localization exceeded 40 Gy in all cases and were identified as conditionally tumoricidal. The estimated mean dose in the projection of the central and lateral subgroups of axillary LNs was lower than the planned dose in two cases: 40 Gy and 35.8 Gy vs. 26.2 Gy and 31 Gy, respectively. It should be emphasized that despite the increase in the depth of the extended tangential fields (10–20 mm in the direction from the chest wall to the lung), the percentage of ipsilateral lung volume irradiated with a total dose of 20 Gy and more was 19% in only one patient, and did not exceed 13% in the other nine cases.

However, the irradiation of pectoral SLNs located on the chest wall at the 3rd and 4th intercostal spaces with a total dose of more than 40 Gy, was achieved only in two cases of using the extended tangential fields. In the remaining eight cases the total dose absorbed in the projection of SLNs defined in this axillary subgroup did not exceed 25.9 Gy.

4. Discussion

Currently, there are at least two randomized trials[10,11] investigating whether surgical dissection in women with early breast cancer without clinical (palpation and US) signs of axillary LN involvement can be omitted and substituted by breast conserving surgery with tangential radiotherapy to the remaining breast tissues. It was assumed that simultaneous irradiation of axillary SLN could be an important part of this treatment strategy that should provide a reliable loco-regional control. In our study we evaluate results of SPECT-CT with radiocolloids and determine high variability of axillary SLN localization. Additionally, with the help of 3D modeling of various radiation fields we demonstrate that standard tangential fields usually do not permit adequate coverage of axillary SLN. On the contrary, extended tangential fields are able to cover SLN in central and pectoral axillary subregions in most cases. Unfortunately, SLN localized in the III-IV intercostal spaces “close to the chest wall” are very rarely covered by any tangential fields and must be irradiated by newer techniques, for example, IMRT. On the basis of this data we propose that in patients that are treated without surgical interventions on axillary LN SPECT-CT visualization of SLN can be an important part of individual radiotherapy planning.

During the last decades, a strong evidence has been obtained that the breast conserving surgery supplemented by tangential radiotherapy to the remaining breast tissue in patients with metastatic involvement of one or two axillary SLNs could achieve high rates of overall and disease-free survival comparable to those obtained after ALND.[12,13]

It was suggested that the high rates of locoregional control (99%) in patients with limited metastatic involvement of axillary LNs (1–2 SLNs) who did not undergo ALND may be associated with post-operative radiotherapy, in particular, with the irradiation of the remaining breast tissues by high tangential fields.[6]

Sentinel LN irradiation in patients with early stage breast cancer without clinical evidence of axillary metastases may be sufficient to achieve a reliable regional control.[10,11] Our data show that with tangential fields irradiation of axillary SLNs located in the projection of central and subpectoral subgroups is possible only in 20% of cases. The literature has also pointed out that standard tangential fields, in most cases, do not allow for adequate irradiation of axillary SLNs.[5,14] However, van Roozendaal et al.[15] determined localization of SLN with the help of SPECT-CT and/or surgical clips and found that with the use of 3D radiotherapy the site of SLN was treated with elective dose in 76% of women. They also mentioned that the size of the breast and body mass index did not influence the dose at the SLN site. Schlembach et al.[7] reported that during standard tangential irradiation the clips placed to mark the location of removed SLNs were encompassed by the 95% isodose in 85% of cases. Similar results have been reported by other authors.[16–18] Nevertheless, Rabinovitch et al.[8] mentioned a significant variability in topography of the removed SLNs which were located at the level of 3–5 thoracic vertebras in 87% of cases and at the level of 6–7 thoracic vertebra in the remaining 13% cases. Alco et al. underlined that only careful planning of tangential field geometry combined with the use of multileaf collimators could increase the mean dose to axillary LNs.[19] Our results of preoperative visualization of SLNs also indicate a substantial variability in their topography: localization of SLNs in the central and pectoral subgroups corresponded to the standard expectations in 61% and 50% of cases, respectively. In addition, modeling of various radiation fields and techniques demonstrated a large variability in the doses absorbed by SLNs of different localization. These data support the proposal that SPECT-CT visualization of SLNs can be a useful tool for radiotherapy planning in women with early breast cancer, especially in those cases when we plan to cover ASLNs by the fields designed for the whole breast irradiation. This option can be especially interesting in women that are treated without surgical sampling of axillary LNs.

Our study has several important limitations. As we did not find any consensus on the division of axillary (level I) LNs into separate subgroups, we used “homemade” classification which was based on vascular anatomy and adopted for the purposes of radiotherapy planning. We designated the subgroup of pectoral LNs “located close to the chest wall” which did not correspond to anatomical classification principals but from our point of view could be important for fields design. Comparison of different radiotherapy techniques was performed after virtual positioning of SLN according to anatomical landmarks (vessels, bony structures, muscles) and subsequent modeling of radiation portals.

5. Conclusion

SPECT-CT visualization of SLNs in women with early breast cancer reveals different variants of their location in the axillary region, which, in turn, affects the opportunity for SLN tumoricidal-dose irradiation using different modifications of tangential fields. Upon detection of “non-standard” SLN localization (in the immediate vicinity of the chest wall or in the projection of the lateral subgroup), the simultaneous irradiation of the remaining breast tissue and axillary SLNs should be performed using more sophisticated radiation therapy techniques, primarily IMRT. After a breast conserving treatment without axillary surgery, simultaneous irradiation of the remaining breast tissue with the axillary SLNs can be performed after SPECT-CT visualization of SLNs as the necessary step in radiotherapy planning.

Financial disclosure

None declared.

Ethical standards

All procedures performed in the study were in accordance with the ethical standards of the Institutional and National Research Committee and with 1964 Helsinki Declaration and its later amendments or comparative ethical standards

Conflict of interest

None declared.

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